

**REMARKS**

Applicants note that all cancellations and amendments presented herein are without acquiescing to any of the Examiner's arguments or rejections, and solely for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),<sup>1</sup> and without waiving the right to prosecute the cancelled claims (or similar claims) in the future.

Applicants note that the "Office Action Summary" page of the Office Action incorrectly indicated that the claims were subject to restriction and/or election and that the period for reply expired one month from the mailing date of the Office Action. A telephone conversation with the Examiner confirmed that the Office Action was not a request for restriction or election and that the proper period for reply expires 3 months from the date of mailing of the Office Action.

In the Office Action dated 4/22/05, the Examiner made several rejections. Each of the rejections is listed below in the order in which they are herein addressed.

I) Claims 10 and 19 are rejected under 35 U.S.C. 101 as allegedly lacking utility;

II) Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite;

III) Claims 1 and 4-15 are rejected under 35 U.S.C. 112, first paragraph as allegedly lacking enablement;

IV) Claims 1, 5, 6, and 14 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Gille et al. (Life Sciences 74:271 [2003]; hereinafter Gille);

V) Claims 1-9, 11-18 and 20 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Dieter et al. (U.S. Patent 6,323,186; hereinafter Dieter);

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<sup>1</sup> 65 Fed. Reg. 54603 (Sept., 8, 2000).

VI) Claims 1-3, 5, 9, and 12-15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Rossomando et al. (Proc. Natl. Acad. Sci 78: 2278 [1981]; hereinafter Rossomando);

VII) Claims 1-9, 11-18 and 20 are rejected under 35 U.S.C. 103(a) as allegedly being obvious in light of Herr (U.S. Patent application 2002/0064849; hereinafter Herr) in view of Gille or McEwen et al; and

VIII) Claims 6, 7, and 16-18 are rejected under 35 U.S.C. 103(a) as allegedly being obvious in light of Herr in view of Rossomando.

**I. The Claims are Supported by a Utility**

The Examiner has rejected Claims 10 and 19 under 35 U.S.C. 101 as allegedly lacking utility (Office Action, pg. 2). Applicants note that Claim 19 has been canceled for other reasons (See below). The Examiner states: "Although this assays shows the effect of a test compound on VC1-ACGC as compared to the effect on VC1-(D396A) ACGC), it is not clear how these results could be extrapolated to normal physiological conditions." The Applicants respectfully disagree and submit that the Examiner has misapplied the Patent Office's own guidelines for determining utility. In particular, the Guidelines state:

"(1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." (M.P.E.P. 2701).

The Applicants submit that they have provided a specific and substantial use for the enzyme of Claim 10 in the form of the assay described in Claim 1. The fact that the mutant enzyme is not found in nature is not relevant to its use in the methods of the present invention. One skilled in the art would recognize that the enzyme described in Claim 10 finds use in the screening of test compounds for their effect on nucleotide cyclase activity (e.g., for research or therapeutic uses) as well as structure function

studies. As such, the Applicants submit that Claim 10 is supported by a specific and substantial utility and request that the rejection be withdrawn.

## **II. The Claims are not Indefinite**

The Examiner has rejected Claims 1-15 under 35 U.S.C. 112, second paragraph as allegedly being indefinite (Office Action, pg. 3). In particular, the Examiner states "Applicants enumerate method steps without clearly pointing out and stating what the claimed method is drawn to." (Office Action, pg. 3). The Applicants respectfully disagree and submit that the claims are definite as written. Nonetheless, in order to further the business interests of the Applicants and while reserving the right to prosecute the original (or similar) claims in the future, the Applicants have amended Claim 1 to refer to a method "for screening test compounds for the ability to modulate nucleotide cyclase activity." The Applicants submit that the amended preamble of claim 1 clearly describes the claimed method. Thus, the claim is definite and the rejection should be withdrawn.

The Examiner has further rejected Claims 12-14 as allegedly being indefinite for the phrases "suspected ligand", "suspected activator" and "suspected inhibitor." In particular, the Examiner states "It is not certain what applicants intend or what qualities they refer by the recitation 'suspected'." (Office Action, pg. 4) The Applicants respectfully disagree and submit that the claims are definite as written. Nonetheless, in order to further the business interests of the Applicants and while reserving the right to prosecute the original (or similar) claims in the future, the Applicants have amended Claims 12, 13, and 14 to refer to a compound suspected of being an activator, ligand or inhibitor. As such, the Applicants submit that the Claim are definite and respectfully request that the rejection be withdrawn.

## **III. The Claims are Enabled**

The Examiner has rejected Claims 1 and 4-15 under 35 U.S.C. 112, first paragraph as allegedly lacking enablement (Office Action, pg. 4). In particular, the

Examiner states: "Claim 1 is incomplete without a control reaction..." (Office Action, pg. 4). The Applicants respectfully disagree and submit that the claims are enabled. The Applicants submit that the absolute measure of fluorescence activity has meaning in determining the effect of a test compound on cyclase activity. The control reaction is not critical or essential to practice the invention. The Examiner has pointed to no evidence to the contrary. The Applicants have taught one of skill in the art how to practice the method of Claim 1 as required under 25 U.S.C 112, first paragraph. Accordingly, the claims are enable and the rejection should be withdrawn.

#### **IV. The Claims are not Anticipated**

The Examiner has issued several rejections under 35 U.S.C. 102(a) and 102(b). Each of the rejections is addressed in detail below.

##### **A. Gille is Not Prior Art**

The Examiner has rejected Claims 1, 5, 6, and 14 under 35 U.S.C. 102(a) as allegedly being anticipated by Gille (Office Action, pg. 5). The Applicants respectfully disagree and submit that Gille is not prior art. The present application claims priority to provisional application 60/447,074, filed 2/13/03 (see specification, page 1, lines 3-4). Gille was published on 12/5/03 (see the internet web site of Science Direct attached hereto). As the provisional application filed on 2/13/03 discloses all of the elements of the Claims, Gille can not anticipate Claims 1, 5, 6, or 14. As such, the rejection should be withdrawn.

##### **B. The Claims are not Anticipated by Dieter**

Claims 1-9, 11-18 and 20 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Dieter (Office Action, pg.5). The Applicants respectfully disagree and submit that Dieter does not teach all of the elements of the claims as required for rejection under 35 U.S.C. 102. In particular, Dieter does not teach the element of a **nucleotide cyclase** enzyme as required by independent Claims 1. Claims 16-20 have been canceled for other reasons (see below). The Examiner has pointed to no teaching in

Dieter of nucleotide cyclase enzymes nor is any present. As such, the Applicants respectfully request that the rejection be withdrawn.

**C. The Claims are not Anticipated by Rossomando**

Claims 1-3, 5, 9, and 12-15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Rossomando (Office Action, pg. 5). The Applicants submit that Rossomando does not teach all of the elements of independent claim 1 as required for rejection under 35 U.S.C. 102. In particular, Rossomando does not teach contacting the nucleotide cyclase and the fluorescently labeled substrate with a test compound. Rossomando further does not teach comparing the level of fluorescence in the presence of the test compound with the level of fluorescence in the absence of the test compound (Claim 2). As such, Rossomando does not anticipate the claims and the rejection should be withdrawn.

**II. The Claims are Non-Obvious**

The Examiner has issued two rejections under 35 U.S.C. 103 (each of the rejections is discussed in further detail below). The Applicants respectfully disagree with the rejections and submit that the examiner has failed to provide a *prima facie* case of obviousness. The combination of references referred to by the Examiner fails to provide a *prima facie* showing of obviousness as required by § 2143 of the Manual of Patent Examining Procedure (MPEP). There are three criteria that must be met to provide *prima facie* obviousness. The first of these criteria is a suggestion or motivation in the references or the knowledge generally available to combine the reference teachings. The second criterion is the prior art must teach or suggest all the claim limitations. The third criteria is a reasonable expectation of success should the combination be carried out. Applicants submit that the Examiner has failed to set forth a *prima facie* case of obviousness because these criteria have not been met.

**A. Claim 1-9, 11-18 and 20 are not obvious**

The Examiner has rejected Claims 1-9, 11-18 and 20 under 35 U.S.C. 103(a) as allegedly being obvious in light of Herr in view of Gille or McEwen (Office Action, pg.

6). The Applicants respectfully disagree. Nonetheless, in order to further the business interests of the Applicants and while reserving the right to prosecute the original (or similar) claims in the future, the Applicants have canceled Claims 16-20.

As described above, Gille is not available as prior art against the present invention. The Examiner has failed to provide the proper citation for McEwen and has not provided the reference. Thus, the Applicants assume that the Examiner is referring to the McEwen reference cited by the Applicants in their Information Disclosure Statement (Analytical Biochemistry, 281:109 [2001]).

**i. The cited references do not provide a motivation to combine the references**

The Applicants respectfully disagree with the rejection and submit that the Examiner has failed to provide a prima facie case of obviousness. In particular, the Applicants submit that the Examiner has failed to provide a motivation to combine the teachings of McEwen with the teachings of Herr. Herr is silent on the use of fluorescent based methods of assaying test compounds. Indeed, Herr indicates that suitable methods are known in the art for assaying adenyl cyclase activity: "cAMP production may be readily measured using methods which are well known in the art..." (paragraph 0059). Herr does not indicate any deficiencies in the art known assay methods. Nor does Herr indicate the need for alternative assay methods. Likewise, McEwen does not suggest that the disclosed fluorescent nucleotide analogs find use in the assay of nucleotide cyclase enzymes.

The Examiner's basic argument appears to be that because the methods of McEwen could, in theory, be applied to Herr, that one would be motivated to make the combination. The courts have repeatedly stated that this is not the proper standard:

"Although the Commissioner suggest that [the structure in the primary prior art reference] could readily be modified to form the [claimed] structure, '[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggest the desirability of the modification.' " *In re Laskowski*, 871 F.2d 115, 10 USPQ2d 1397 (Fed Cir. 1989).

Although a prior art device "may be capable of being modified to run the way [the patent applicant's] apparatus is claimed, there must be a

suggestion or motivation in the reference to do so." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed Cir. 1990)

The Examiner thus appears to *assume* that such motivation exists in the "general knowledge," without providing any basis for such an assumption. As discussed above, however, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

[t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

*In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statement that the cited references in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

The Office has also failed to analyze the invention as a whole. When analyzed as a whole, the fluorescent based nucleotide cyclase assay of the present invention is non-obvious. "That each element in a claimed invention is old or unpatentable does not determine the nonobviousness of the claimed invention as a whole." *Custom Accessories v. Jeffrey-Allan Industries Inc.*, 807 F.2d 955, 1 USPQ 2d 1196, 1198 (Fed. Cir. 1986); See also *Brantingson Fishing Equipment Co. v. Shimano American Corp.*, 9 USPQ 2d 1669, 1672 (Fed. Cir. 1988). Put another way: "Only God works from nothing. Men must work with old elements." *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 225 USPQ 26, 31 n. 3 (Fed. Cir. 1985) (quoting from Markey, "Why Not the Statute," 65 JPOS 331, 333-334 (1983)).

The *Fromson* case is particularly relevant here. In that case, the inventor developed a process for photolithography using 1) aluminum as a substrate, 2) oxide coatings by anodization, 3) silication, and 4) application of light-sensitive resins. The district court correctly found that each of these elements individually were known in the art - but incorrectly concluded, on the basis of the unpatentability of each element, that

the combination of these steps was unpatentable. On appeal, the Federal Circuit pointed to the "fundamental error" of the district court, noting: "At no point did the court indicate, nor does the record indicate, a basis on which it can be said that the making of that combination would have been obvious when it was made." *Fromson, supra* at 31.

Likewise, in the instant case there has been no showing of why one would be motivated to use the nucleotide analogs of McEwen in combination with the enzyme of Herr. Absent a motivation to combine the references, the Examiner has not established a *prima facie* case of obviousness.

It therefore appears that the Examiner is attempting to find the required motivation to combine the cited references in Applicants' own specification rather than in the cited art. Specifically, to arrive at the presently claimed invention, one of ordinary skill in the art would have had to have been motivated to: (I) choose the nucleotide analogs of McEwen, while ignoring the fact that this reference says nothing about (and, indeed, is not at all concerned with) assaying nucleotide cyclase activity; and combine these elements with (II) the nucleotide cyclase enzyme of Herr, while ignoring the fact that Herr specifically does not teach the need for additional detection methods. Without using the presently claimed invention and the present specification as the blueprint for this hindsight picking and choosing the isolated elements of each reference, one of ordinary skill in the art would have found no specific suggestions to include one element and exclude another from each of the cited references to produce the presently claimed invention. Without such suggestions in the cited art, the combination of the cited references as the Examiner has done is nothing more than a hindsight obviousness analysis.

As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than



the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure."). The Board has also provided the same mandate on this issue:

it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

*Ex parte Haymond*, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness. Applicants also are well-aware of the often-cited language in the MPEP that:

[a]ny judgement [sic] on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

MPEP § 2145(X)(A) (quoting *In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (C.C.P.A. 1971)). This boilerplate from the MPEP, however, does not negate the Examiner's burden of providing *specific* evidence or knowledge that would have motivated one of ordinary skill to have modified the cited references and combine their respective disclosures so as to arrive at the presently claimed invention. As noted above, such specific evidence or knowledge has not been provided by the Examiner; hence, the boilerplate language from the MPEP is of no avail in the present case.

Moreover, it is axiomatic that, in order to support a *prima facie* case of obviousness, the prior art must suggest making the *specific* molecular modifications necessary to achieve the claimed invention. See *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lahu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). That is, simply because "one can conceive a general process in advance for generating an *undefined* method [*e.g.*, assaying a nucleotide cyclase enzyme] does not mean that a claimed *specific* method [*e.g.*, the specific methods of the presently claimed invention] was precisely envisioned and therefore obvious." *Deuel* at 1559. Thus, in order for McEwen and Herr to be suitable as primary references upon which to base a *prima facie* case of obviousness, there must be, at a minimum, a teaching or suggestion in these references or elsewhere that would have compelled one of ordinary skill in the art to include all of the elements of the presently invention in the combination of the presently claimed invention. As noted above, such a teaching or suggestion is wholly lacking in McEwen and Herr. Therefore, the cited references taken together are seriously deficient (particularly in view of the holding in *Deuel*), and cannot support a *prima facie* case of obviousness.

Applicants submit that, upon careful analysis of the cited references, the skilled artisan would have found no motivation to combine or modify the disclosures of the references to arrive at the presently claimed invention. Accordingly, a *prima facie* case of obviousness has not been established. Therefore, the rejection of the present claims under 35 U.S.C. § 103(a) is in error, and Applicants respectfully request that it be reconsidered and withdrawn.

**ii. The cited References do not teach all of the elements of the presently claimed invention**

In addition, the Applicants submit that even if the references are improperly combined, the cited references do not teach all of the elements of the presently claimed invention. For example, neither McEwen nor Herr, alone or in combination teach the claim elements of the nucleotide cyclase enzyme being a guanylyl cyclase (Claim 4); the nucleotide cyclase enzyme being an orphan receptor (Claim 7); a high-throughput method (Claim 11); or a membrane bound nucleotide cyclase (Claim 15). As such, the Applicants request that these claims be passed to allowance.

**B. Claim 6, 7, and 16-18 are Non-Obvious**

The Examiner has rejected Claims 6, 7, and 16-18 under 35 U.S.C. 103(a) as allegedly being obvious in light of Herr in view of Rossomando (Office Action, pg. 8). Claims 16-18 have been canceled for other reasons. Applicants note that the Examiner has only applied the instant rejection to dependent Claims 6 and 7. Applicants note that, by definition, Claims 6 and 7 include the elements of independent Claim 1.

The Applicants submit that the Examiner has failed to provide a motivation to combine the teachings of Rossomando with the teachings of Herr. Herr is silent on the use of fluorescent based methods of assaying test compounds. Indeed, Herr indicates that suitable methods are known in the art for assaying adenylyl cyclase activity: "cAMP production may be readily measured using methods which are well known in the art..." (paragraph 0059). Herr does not indicate any deficiencies in the art known assay methods. Nor does Herr indicate the need for alternative assay methods. Likewise, McEwen does not suggest that the disclosed fluorescent nucleotide analogs find use in the assay of soluble or orphan nucleotide cyclase enzymes as required by Claims 6 and 7.

The Examiner's basic argument appears to be that because the methods of Rossomando could, in theory, be applied to Herr, that one would be motivated to make the combination. As described above, this is not the proper standard for obviousness rejections. The Applicants further submit that the Examiner has used improper hindsight reconstruction (See above description).


The Applicants further submit that neither Rossomando nor Herr, alone or in combination, teach all of the elements of the claims as required for rejection under 35 U.S.C. 103. For example, neither Rossomando nor Herr, alone or in combination, teach the claim elements of an orphan receptor as required by Claim 7.

The Applicants submit that the Examiner has failed to provide a prima facie showing of obviousness. As such, the rejection should be withdrawn.

**CONCLUSION**

If a telephone interview would aid in the prosecution of this application, the Examiner is encouraged to call the undersigned collect at (618) 218-6900.

Date: July 22, 2005



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Tanya A. Arenson  
Registration No. 47,391

MEDLEN & CARROLL, LLP  
101 Howard Street, Suite 350  
San Francisco, California 94105  
(608) 218-6900